2.0 Scientific abstract

The adenovirus E1A is a gene that is expressed in the early part of viral replication. E1A can induce apoptosis and downregulation of HER-2 overexpression, which results in suppression of tumorigenicity.

There is no consensus for the treatment of "platinum-refractory" or "platinum-resistant" ovarian cancer, a class of individuals who are particularly challenging to treat. Prognosis is poor, and treatment is primarily palliative in nature. Responses to a variety of single chemotherapeutic agents, as well as to a combination of agents in largely phase II trials have been similar, ranging from 10-35% (Markman and Bookman, 2000). IV paclitaxel, given alone or in combination with other agents is a standard treatment for subjects who have relapsed. In an attempt to increase the dose intensity of paclitaxel therapy, weekly IV paclitaxel has been recommended. This treatment schedule is well tolerated, but the response rate in heavily pretreated subjects is still only 28.9% (Abu-Rustum *et al.*, 1997).

Given that this group of subjects is poorly responsive to conventional chemotherapy, and consequently has limited options, an alternative approach to treatment is warranted. The use of a gene therapy agent with anti-tumor effects and the ability to sensitize cancer cells to traditional chemotherapy is appealing.
The peritoneal cavity is a common site of tumor recurrence after initial "radical" surgical treatment of ovarian malignancies. Dissemination in this cavity is often widespread. Because of the unusual natural course of ovarian cancer (characterized by its tendency to be confined to the peritoneal cavity), control of metastatic disease in the peritoneal cavity is an important and challenging problem, which can be improved by direct delivery of drug into the peritoneal cavity (Los and McVie, 1990).

The primary objectives of the proposed protocol are to evaluate toxicity and establish the maximum tolerated dose (MTD) of intraperitoneal (IP) tgDCC-E1A in combination with intravenous (IV) paclitaxel and to measure tumor response of intraperitoneal (IP) tgDCC-E1A in combination with intravenous (IV) paclitaxel and compare to intravenous (IV) paclitaxel alone. The secondary objectives are to measure time to progression and overall survival and to examine the biological effects of combined tgDCC-E1A and paclitaxel in ovarian cancer cells as measured by laboratory testing.

The rationale for this study stems from the fact that the E1A acts as an antineoplastic agent by impacting the cellular pathways in tumor cells. Treatment with E1A gene therapy alone can reduce tumor growth and increase survival in animal models of human cancers. One of the key outcomes of expressing E1A in tumor cells is its ability to increase the sensitivity of neoplastic cells to conventional chemotherapeutic drugs. Data from murine models further support these *in vitro* studies and have demonstrated that when used together, chemotoxic agents and tgDCC-E1A have a greater anti-tumor effect than either treatment alone.

The mechanism of how E1A induces this sensitivity is unclear. However, conventional chemotoxic drugs interfere with the cellular machinery controlling the cell cycles and affecting the molecular pathways that mediate apoptosis (Hickman 1996). These pathways are fundamentally perturbed in cancer cells as a result of neoplastic

transformation (Fearon and Vogelstein 1997). During treatment with chemotherapeutic drugs, however, neoplastic cells may become resistant to the chemotoxic effects. Specific oncogenes and alterations of tumor suppressor genes are associated with this loss of chemosensitivity (Ruley 1997). For example, overexpression of the HER-2/*neu* oncogene correlates inversely with cisplatin sensitivity in ovarian cells.

The tumor inhibitor protein E1A enables cells to more efficiently engage the cellular apoptotic machinery. A recent study has genetically defined at least two E1A functions that act in concert to promote apoptosis and chemosensitivity (Samuelson and Lowe 1997). E1A interacts with the p300/CBP protein, which is known to physically associate with the p53 oncogene and to contribute to its transcriptional activity. Binding of E1A to p300 modulates p53 function and induces apoptosis. A second mechanism whereby E1A increases chemosensitivity is the inactivation of the RB tumor suppressor gene (Samuelson and Lowe 1997).

Some cancer cells are deficient in p53, however, and in many human cancers the RB gene is mutated and its pathway disrupted (Weinberg 1995). Thus, it would be expected that expression of E1A would not contribute to the induction of chemosensitivity in RB-deficient cells (Samuelson and Lowe 1997) or in p53-deficient cells. Nevertheless, E1A can sensitize RB mutant and p53-deficient cancer cells to the induction of apoptosis by standard chemotherapeutic agents, via other pathways or mechanisms (Teodoro, Shore et al. 1995). Other studies have also demonstrated chemosensitization of cancer cells by ectopic expression of E1A (Frisch and Dolter 1995; Sanchez-Prieto, Quintanilla et al. 1996; Ueno, Yu et al. 1997).

Clinical trials have been conducted at Targeted Genetic Corporation (Seattle, WA) to evaluate the safety and biological activity of tgDCC-E1A alone and in combination with chemotherapy for treatment of ovarian cancer. Two phase I single agent clinical trials (Protocols E1A-9601 and C LF 16 0519 9602) have shown that intraperitoneal tgDCC-E1A infusions are safe and well tolerated with a defined dose-limiting toxicity. A phase I trial of tgDCC-E1A in combination chemotherapy (Protocol 09A01) is currently nearing completion, and shows that intraperitoneal is well-tolerated when administered with intraperitoneal cisplatin and intravenous paclitaxel.

In response to the changing standard of care for ovarian cancer, The University of Texas M. D. Anderson Cancer Center is expanding its evaluation of tgDCC-E1A to include administration with intravenous chemotherapy for women with recurrent ovarian cancer. The proposed phase I/II randomized study of tgDCC-E1A and paclitaxel for women with recurrent, platinum-resistant ovarian cancer, will be performed through funding from a National Cancer Institute Specialized Program of Research Excellence (SPORE) grant. In addition to evaluating the toxicity and establishing the MTD of tgDCC-E1A with paclitaxel, this study will also explore the efficacy and biological activity of the combination, which will help determine if the additive anti-tumor effects of tgDCC-E1A and chemotherapy seen *in vitro* and *in vivo* translate into clinical benefit for ovarian cancer patients.